FATNESS AND FITNESS WITH CARDIO-METABOLIC RISK FACTORS IN ADOLESCENTS

Denise L. Demmer, Lawrence J. Beilin, Beth Hands, Sally Burrows, Kay L. Cox, Wendy H. Oddy, Trevor A. Mori

The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: April 11, 2017
Accepted: September 13, 2017
First Online: October 27, 2017

The Journal of Clinical Endocrinology & Metabolism; Copyright 2017 DOI: 10.1210/jc.2017-00851

Fatness vs. fitness with cardio-metabolic risk

FATNESS AND FITNESS WITH CARDIO-METABOLIC RISK FACTORS IN ADOLESCENTS

Denise L. Demmer[1], Lawrence J. Beilin[1], Beth Hands[2], Sally Burrows[1], Kay L. Cox[1], Wendy H. Oddy[3], Trevor A. Mori[1]

[1]*School of Medicine and Pharmacology, Royal Perth Hospital Unit, The University of Western Australia, Perth, Australia*

[2]*Institute for Health Research, The University of Notre Dame Australia, Perth, Australia*

[3]*The Menzies Institute for Medical Research, The University of Tasmania, Hobart, Australia*

Received 11 April 2017. Accepted 13 September 2017.

Context: The relative importance of fitness and fatness with cardio-metabolic risk factors are uncertain during the crucial developmental stage of late adolescence.
Objective: We aimed to compare the concurrent influences of cardiorespiratory fitness and fatness in relation to cardio-metabolic risk factors in adolescents from the Western Australian Pregnancy Cohort Study.
Design, Setting and Participants: Cross-sectional analysis was performed on 1128 participants with complete blood pressure data and 963 participants with complete blood biochemistry at 17 years of age. Fatness (waist circumference) and cardiorespiratory fitness (PWC_{170}) were assessed as continuous measures to avoid the use of arbitrary cut points. Analyses used linear regression models adjusted for sex and potential lifestyle confounders.
Main Outcome Measure: Cardio-metabolic risk factors.
Results: Fatness was positively associated with systolic BP (coefficient: 0.19; p<0.001; beta coefficient: 0.20), triglycerides (log coefficient: 0.009; p<0.001; beta coefficient: 0.24), LDL-C (coefficient: 0.005; p=0.007; beta coefficient: 0.10) and hs-CRP (log coefficient: 0.05; p<0.001; beta coefficient: 0.35). There were no significant effects of fitness on any of these measures. A positive association between HOMA-IR and fatness (log coefficient: 0.02; p<0.001; beta coefficient: 0.33) was attenuated by fitness (log coefficient: -.0.18; p<0.001; beta coefficient: -0.18). Fatness was inversely associated with HDL-C in both sexes (coefficient: -0.006; p<0.001; beta coefficient: -0.23), while fitness was positively associated with HDL-C only in females (coefficient: 0.08; p=0.03; beta coefficient: 0.15).
Conclusions: The adverse effects of central adiposity seen across a broad range of cardio-metabolic risk factors were only partially ameliorated by fitness in this adolescent population.

We studied the concurrent influences of fatness and fitness with a range of cardio-metabolic risk factors in an adolescent population and found that fatness had greater effects compared to fitness.

INTRODUCTION

The prevalence of all-cause mortality, cardiovascular disease (CVD) and Type II diabetes among overweight adults is attenuated in individuals with a moderate-to-high level of cardiorespiratory fitness (hereafter fitness) suggesting that fitness offers a degree of protection in overweight individuals (1,2). The fat but fit hypothesis as expressed by Blair et al.(3) stated that a moderate-to-high level of fitness may attenuate or eliminate the risk of cardiovascular and metabolic disease, independent of body mass index (BMI). Obesity is a major health problem that affects

children and adolescents. Adults who were overweight in childhood have a higher blood pressure (BP), fasting lipids and insulin levels, and increased risk of CVD, compared to adults who were not overweight as children (4). Childhood and adolescence are crucial periods during which dynamic changes in various metabolic systems, including hormonal regulation, body fat content and body fat distribution occur during puberty and growth (5). Similarly, lifestyle and healthy or unhealthy behaviours are established during adolescence, which may persist into adult life and influence later health status (6). Understanding the influence of cardiorespiratory fitness on the development of obesity-associated cardio-metabolic risk factors is important for developing strategies for the prevention of CVD in adulthood. Low levels of fitness and increased adiposity often occur in combination. However, the relative importance of fitness and fatness on cardio-metabolic risk factors is unclear, particularly during adolescence.

Previous studies examining the effect of fitness and fatness on cardio-metabolic risk factors in children and adolescents have used different methodologies and outcomes and have generally categorised fatness and fitness using arbitrary cut points, which can lead to the misclassification of individuals(7-10). Moreover, most studies have used BMI as a measure of fatness, which may have inherent limitations as it does not take into account lean body mass, nor does it specify the degree of central adiposity, which has been linked to increased risks of metabolic disease (11). In this regard, a measure of central obesity, such as waist circumference may be more relevant. The aim of the present study was to examine cardiorespiratory fitness and fatness, as continuous variables, in relation to cardio-metabolic risk factors in a large population of from the Western Australian Pregnancy (Raine) Cohort Study at age 17 years. We hypothesised that fitness would either ameliorate or eliminate the adverse effects of fatness on a range of cardio-metabolic risk factors and that the effects would be similar in boys and girls.

METHODS

Participants

The Western Australian Pregnancy Cohort (Raine) Study is a prospective population study that recruited 2900 pregnant women between 16 to 20 weeks gestation from King Edward Memorial Hospital and closely located practices, in Perth, Western Australia from 1989 to 1992 (12). The mothers gave birth to 2868 live infants. The offspring have been followed at approximately three year intervals with a range of anthropometry measurements, BP, lifestyle and psychosocial factors and detailed biochemistry related to cardio-metabolic risk. Ethics approval for the 17 year assessments was obtained from the Human Research Ethics Committee at the University of Western Australia, Curtin University and Princess Margaret Hospital. Written informed consent was obtained from the participant's parent and the participant. This analysis uses data from the 17-year follow-up of the offspring conducted from 2006-2008. The 17-year survey included participants with complete measures of blood pressure, waist circumference and fitness (n=1128) or complete measures of blood biochemistry, waist circumference and fitness (n=963).

Anthropometry

Waist circumference was measured at the umbilicus level with a metal tape measure (to the nearest 0.1 cm). Obese individuals were identified as having a waist circumference >90th percentile as defined by the National Health and Nutritional Examination Survey (13). Height was measured by a wall mounted Stadiometer (to the nearest 0.1 cm) and body weight was measured using a Wedderburn Chair Scale (to the nearest 100g) with participants dressed in light clothes. Individuals with a high BMI as defined by the Centres for Disease Control and Prevention Growth Charts were identified as having a BMI >90th percentile (14).

Cardiorespiratory fitness

Fitness was estimated from heart rate recordings during sub-maximal cycle ergometry using the Physical Work Capacity Protocol (PWC_{170}) (Monark cycle ergonometer). PWC_{170} is the maximal steady state power attained for a heart rate of 170 beats per minute on a cycle ergometer (15). Participants cycled at an initial workload of 25 watts (W) and aimed to work at a rate of 50-60 rpm for 2 minutes each at 2 successively increasing but submaximal workloads of 25 W increments. PWC170 was assessed by linear regression with extrapolation of the line of best fit to a heart rate of 170 beats per minute. Fitness was adjusted for body weight to normalise the effects of body size on workload output. To identify those with low, middle and high fitness levels, participants were grouped into tertiles of fitness groups.

Biochemistry

Venous blood samples were taken after an overnight fast and analysed in the PathWest Laboratory at Royal Perth Hospital for serum glucose, insulin, total cholesterol, triglycerides, high density lipoprotein-cholesterol (HDL-C) and hs-CRP (high sensitivity C-reactive protein). Low density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula (16). An adverse lipid profile as defined by the National Cholesterol Education Program Expert Panel on Cholesterol Levels in Children was identified as having triglycerides > 1.13 mmol/L, HDL-C <1.04 mmol/L and LDL-C > 3.36 mmol/L (17). The homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated using the formula: fasting insulin (µU/ml) x fasting glucose (mmol/L) / 22.5 (18).

Blood pressure

Systolic BP and diastolic BP were measured using an oscillometric sphygmomanometer (DINAMAP vital signs monitor 8100, DINAMAP XL vital signs monitor or DINAMAP ProCare 100; GE Healthcare) after resting in a supine position for 5 minutes and using the appropriate cuff size on the right arm. Six BP readings were obtained every 2 minutes and the average BP was calculated using the last five readings. BP was recorded on a separate day to the PWC_{170} assessment. Prehypertensive and hypertensive individuals were grouped together and defined as non-sex-specific systolic BP ≥90th percentile.

Demographic and socio-behavioural features

Socio-behavioural data were assessed via a computer-based questionnaire. Alcohol consumption included the type (beer, spirits or wine) and amount (can, stubby, nip, glass or standard drink) of alcoholic beverages consumed daily during the previous 7 days. Alcohol consumption was defined as the average number of standard drinks consumed per day, where 1 standard drink equates to 10 g of ethanol. A drinker was a consumer of alcohol at any level during the previous week. Smoking status was assessed from the number of cigarettes smoked each day during the previous 7 days. Oral contraceptive (OC) use in girls was defined by a Yes or No answer to the question, 'In the last 6 months, have you taken any prescription medication(s) e.g. the Pill?' and 'if yes, which medication(s), and are you still taking it?'). Dietary data were collected from a validated 212-item food frequency questionnaire developed by the Commonwealth Scientific and Industrial Research Organisation, Adelaide, Australia. Two dietary patterns ('Western' and 'Healthy') were identified using factor analysis (19). Details of the methodology, the reliability and the validity of this food frequency questionnaire have been previously published (20). Annual family income was categorised as Australian dollars ≤ 35 000 (low family income), 35 001 to 78 000 (middle family income) and ≥ 78 001 (high family income) at 17 years from 2006 to 2009.

Statistical analyses

Descriptive data were summarised by sex using means, geometric means, percentages and 95% CI's. Waist circumference was assessed as the fatness measure and PWC_{170} as the fitness measure. These two measures were assessed as continuous variables to avoid the use of arbitrary cut points. Risk factors were assessed for normality and log transformed if substantial departures from normality were found. For the outcome of hs-CRP, values >10 were excluded as being likely due to incidental illness. In view of the potential effect of OC use on blood pressure and lipids a 3 level sex variable (females not using OC, females using OC and males) was created to assess the effect of OC use in the final multivariable models. If no significant difference was detected between the two female groups, a two level sex variable (females, males) was included. Potential confounding factors included alcohol use, smoking, dietary pattern and family income. Associations with fatness and fitness were assessed using linear regression or Tobit regression if the outcome was censored at the lower limit of an assay (21). Logistic regression was employed examining the outcome of pre-hypertension and hypertension. Potential non linearity of associations was investigated initially by Lowess plots and then using fractional polynomials. With the exception of Tobit regression, all models included a variance adjustment for siblings within a family. Maximum likelihood estimation was used to retain individuals with missing confounder data in the analysis, resulting in unbiased estimates when missing data was missing at random. Tobit regression models were adjusted for confounding variables but only for those participants with complete data on all confounders. We also investigated the interactions between sex and the effects of fatness or fitness on each cardio-metabolic risk factor. Interactions were excluded from the model if $p>0.05$. Initial models were adjusted for sex and extended models further adjusted for potential lifestyle confounders, unless Tobit regression was employed. Standardised beta coefficients for fatness and fitness were used to provide comparable measures of the effect size. Beta coefficients were only provided for significant associations. Three-dimension surface plots were generated using SAS software (V9.4 SAS Institute Inc., Cary. NC, USA) for those models where both fitness and fatness were significant or where significant interactions with sex were detected. Stata MP Version 13 (Stata Corp, College Station, TX) was used for statistical analysis. All reported p values are 2-tailed and significance was set at $\alpha=0.05$.

RESULTS

Descriptive characteristics

At 17 years of age, compared with females, males were heavier, had a larger waist circumference, were fitter and had higher systolic BP and mean blood glucose ($p<0.001$) (Table 1). Mean BMI was similar between the sexes. Females had significantly higher mean cholesterol, HDL-C, LDL-C, insulin, hs-CRP and diastolic BP than males. Using non sex-specific criteria, the proportion of pre-hypertensive or hypertensive individuals were similar between males and females (16.7% versus 15.2 %, $p=0.63$). Approximately 14% of females used OC and 50% of participants consumed alcohol at any level within the previous week. A comparison of the 1,131 study participants with data used in any of the analyses (i.e. with waist circumference and physical activity, and either blood pressure or biochemistry), with those 1,737 individuals that did not participate in the 17-year follow-up, shows that those who did not participate were more likely to have a lower family income (46.3% vs 34.3%), a shorter gestational age (273.3 days vs 275.3 days), a shorter birth length (48.7 cm vs 49 cm) and lower birth weight (3256.8g vs 3329.7g), but similar maternal weight and height at the 18th week of pregnancy, (Supplementary

Table 1). The original cohort comprised of 88% Caucasians, which is representative of the Western Australian population.

Independent associations between fatness and fitness with cardio-metabolic risk factors

Blood Pressure

In model 1 adjusting for sex and OC use, fatness was positively associated with systolic BP (coefficient: 0.19; p<0.001) (Table 2, Model 1, Figure 1a). Fatness beta coefficient of 0.20 indicates for a change of fatness of 1 standard deviation (11.2 cm), systolic BP will change by 2.0 mmHg. After adjusting for additional potential confounders, systolic BP remained positively associated with fatness (coefficient: 0.18; p<0.001; beta coefficient: 0.2) (Table 2, Model 2). Fitness was not associated with systolic BP in the unadjusted or the confounder adjusted model. Fatness was not significantly associated with diastolic BP whereas fitness was inversely associated with diastolic BP (coefficient: -1.57; p<0.001; beta coefficient: -0.16) (Table 2, Model 1). Fitness beta coefficient of -0.16 indicates for a change of fitness of 1 standard deviation (0.6 W/kg), diastolic BP will change by -1.0 mmHg. Further adjustment for lifestyle factors did not substantially change the coefficients nor did they vary by sex (Table 2, Model 2). Fatness was significantly associated with pre-hypertension/hypertension status in both sexes (odds ratio: 1.03, p=0.001) (Supplementary Table 2), whereas fitness was not associated with pre-hypertension/hypertension status in either sex.

Fasting lipids

Fatness was inversely associated with HDL-C in both males and females (coefficient: -0.006 p<0.001) (Table 3, Model 1, Figure 1b). Fitness was positively associated with HDL-C in females only (coefficient: 0.08; p=0.03). The standardised beta coefficients showed that in females, fatness had a greater effect on HDL-C (beta coefficient: -0.23) compared with fitness (beta coefficient: 0.15). In other words, the fatness beta coefficient of -0.23 indicates for a change of fatness of 1 standard deviation (11.2 cm), HDL-C will change by -0.07 mmol/L, whereas the fitness beta coefficient of 0.15 indicates for a change of fitness of 1 standard deviation (0.6 W/kg), HDL-C will change by 0.04 mmol/L. The differential association between fatness and fitness relative to HDL-C in males and females are illustrated in Figure 2. These findings did not change after the inclusion of potential confounders (Table 3, Model 2).

Fatness was positively associated with triglycerides (log coefficient: 0.009, p<0.001; beta coefficient: 0.24) (Table 3, Model 1) and LDL-C in both sexes (coefficient: 0.005, p=0.007; beta coefficient: 0.10) (Table 4, Model 1). Fatness beta coefficients of 0.24 and 0.10 for triglycerides and LDL-C respectively, indicates for a change of fatness of 1 standard deviation (11.2 cm), triglycerides will change by 0.10 mmol/L and LDL-C by 0.06 mmol/L. These associations were not altered after the inclusion of potential confounders (Table 3, Model 2: Table 4, Model 2). Fitness was not associated with either triglycerides or LDL-C in unadjusted or adjusted analyses. Neither fatness nor fitness was significantly associated with cholesterol in both unadjusted and adjusted models (Table 4), although fatness almost reached significance.

HOMA-IR and hs-CRP

Fatness was positively associated with HOMA-IR (log coefficient: 0.02; p<0.001) after adjusting for sex (Table 5, Model 1, Figure 1c), whereas fitness was inversely associated with HOMA-IR (log coefficient: -0.18; p<0.001). The standardised beta coefficients showed that fatness had a greater effect on HOMA-IR (beta coefficient: 0.33) compared with fitness (beta coefficient: -0.16). The fatness beta coefficient of 0.33 indicates for a change of fatness of 1 standard deviation (11.2 cm), HOMA-IR will change by 1.85. Whereas the fitness beta coefficient of -

0.16 indicates for a change of fitness of 1 standard deviation (0.6 W/kg), HOMA-IR will change by -0.30. These effects did not vary by sex. The differential associations between log HOMA-IR and fitness and fatness are illustrated in Figure 3. After further adjustment for lifestyle factors, these effects were unchanged (Table 5, Model 2). Fatness was positively associated with hs-CRP in both sexes (log coefficient: 0.05, $p<0.001$; beta coefficient: 0.35) (Table 5, Model 1). Fatness beta coefficient of 0.35 indicates for a change of fatness of 1 standard deviation (11.2 cm), hs-CRP will change by 0.63 mg/L. This association was not altered after the inclusion of confounders (Table 5, Model 2). Fitness was not associated with hs-CRP in either model.

DISCUSSION

Our results have shown that the adverse effects of fatness, measured as waist circumference, are substantially greater than any beneficial effects of fitness, on a wider range of cardio-metabolic risk factors, in this adolescent population. Fatness had a strong positive effect on systolic BP, triglycerides, LDL-C, HOMA-IR, hs-CRP and was inversely associated with HDL-C. In contrast, fitness was inversely associated with diastolic BP, and HOMA-IR in both sexes, and was positively associated with HDL-C only in females. Although fitness attenuated the adverse effects of fatness on HOMA-IR and HDL-C, fatness had generally stronger effects on most cardio-metabolic risk factors. The lack of an effect of fitness on systolic BP is unexpected but perhaps explained by the dominant effect of fatness. However, the inverse association between fitness and diastolic BP is relevant in view of the fact that diastolic BP may be more predictive of cardiovascular risk in younger individuals (22). Possible mechanisms for the moderating effect of fitness on adiposity related insulin resistance and dyslipidemia include increased muscle mass leading to improved insulin sensitivity and lipoprotein profiles, while reduced diastolic BP is likely to result from exercise/fitness related adaptations of pre-resistance and resistance vessels (23). Thus our findings provide an alternative viewpoint of the 'fat but fit' hypothesis at this critical age of development.

In view of the fact that adolescent activity-related behaviours and obesity track to adult life (24) and predict adult diabetes and coronary disease (25), the significant positive effects of fitness, particularly on adiposity related insulin sensitivity, HDL-C and diastolic BP, would be relevant to reducing the development of Type II diabetes and hypertensive CVD (26). Results from the CARDIA (Coronary Artery Risk Development in Young Adults) study demonstrated increasing fitness over a 15 year period was associated with reduced risk for developing Type II diabetes and the metabolic syndrome, but was not associated with hypertension or hypercholesterolemia (27).

Previous studies examining the 'fat but fit' hypothesis in paediatric populations have used diverse measures of fatness, differing categories of fitness and fatness groups and different CVD risk scores determined from arbitrarily selected risk factors. For example, Jago et al (28) examined quintiles of fitness (shuttle run tests) and fatness (BMI) separately for males and females, in U.S. children aged 12 years. They showed fatness had stronger associations with an adverse cardiovascular profile (28). Ondrak et al. (29) also reported that fatness (as percentage body fat using sum of skinfolds) was a stronger predictor of an adverse cardio-metabolic risk score than fitness among a cohort of 1,824 white and African youth (aged 8-10, 11-13, and 14-16 years). A higher BMI level was associated with a greater risk of being hypertensive in both unfit and fit, in 5,464 males and 8,093 females aged 15-20 years (30).

The European Youth Heart Study showed that individuals within the 'high fitness' group attenuated the negative consequences of total and central adiposity on BP in 873 children aged 9-

10 years (31), and HOMA-IR and fasting insulin in 873 girls aged 9.6 years (32). Reports from the ACLS cohort (8,10) have examined associations between fitness and fatness on cardiovascular risk factors by categorising adolescents using median split, tertiles, quartiles, or clinical cut points, separately for males and females. Overall the results show significant differences in cardio-metabolic risk factors at the extremes of low vs. high fitness or normal weight vs. overweight/obese. Within BMI categories, the low fit individuals exhibited a higher metabolic syndrome score, compared to the high fit subjects.

Strengths of our study include the large population-based sample within a narrow age band that has examined sex differences in post pubertal individuals. These analyses were conducted at 17 years of age when potential confounders such as smoking, drinking and OC use were becoming established behaviours, and the multiplicative effects of these potentially confounding lifestyle factors could be accounted for. As BMI cannot differentiate between lean and fat mass, the use of waist circumference in our study may be more discriminating Indices of central adiposity better estimate a wide range of cardio-metabolic risk factors in other paediatric populations (33,34). Fatness and fitness were analysed as continuous variables which overcomes arbitrary categories that may obscure relative effects of fatness and fitness on cardiovascular risk. In addition, the potential misclassification bias of individuals into obesity and fitness groups is reduced, as cut points used to define these categories are derived from the study populations investigated. Cardio-metabolic risk factors were examined as continuous and separate outcomes which overcomes the limitation of using an arbitrary CVD risk score to express the clustering of main components of adult CVD; as no clear definition of the metabolic syndrome exists within the paediatric population. Limitations of our study include the cross-sectional study design which cannot infer causal relationships. The use of a submaximal exercise test may be a limitation as it is less accurate than measuring the VO_2max of an individual using a maximal exercise test. The latter is considered the gold standard, particularly at lower and higher levels of physical activity (35). The use of a food frequency questionnaire to determine dietary habits has limitations such as under-reporting, reporter bias due to confusion about serving sizes and reliance on memory (36). A further limitation may be some of the relatively small regression coefficients. However, the fatness and fitness coefficients for HDL-C in particular, are likely to be underestimates of true effects due to 'regression dilution bias'. The coefficients for HOMA-IR, systolic BP and hs-CRP are more substantial and show the relative contribution of fatness and fitness to each cardio-metabolic risk factor.

Our findings have significance in view of the obesity epidemic and sedentary habits being established during childhood and adolescence. We have shown that fitness only partially ameliorated the adverse effects of adiposity on selected cardio-metabolic risk factors, thus providing some support for the 'fat but fit' hypothesis. Nevertheless the importance of physical activity and fitness at this age should not be downplayed in view of their known contribution to prevention and management of obesity (37), and the wide ranging benefits of physical activity for physical and mental health over and beyond measures of cardio-metabolic risk factors (38-40). As fitness alone cannot completely reduce the adverse effects of central obesity, it is crucial that healthy eating patterns conducive to avoiding adiposity along with physical activity continue to be the two pillars of public health programs, to reduce the risk of obesity-related co-morbidities in adolescence and later life.

Acknowledgments

We thank the Raine Study participants, their families, and the Raine Study Team for cohort co-ordination and data collection.

Address all correspondence and requests for reprints to: Denise Demmer, School of Medicine and Pharmacology, Royal Perth Hospital Unit, University of Western Australia, GPO Box X2213, Perth, Western Australia 6847, Australia. Telephone: +61 8 92240343 Fax: +61 8 92240243 E-mail: denise.demmer@uwa.edu.au

This work was supported by the National Health & Medical Research Council program (grant number 353514) and project (grant number 403981) grants. Core management of the Raine Study is funded by the University of Western Australia (UWA); the Raine Medical Research Foundation; the Telethon Institute for Child Health Research; the UWA Faculty of Medicine, Dentistry and Health Sciences; the Women and Infants Research Foundation, Curtin University and the Royal Perth Hospital Medical Research Foundation. The funding source had no role in the planning, analysis or writing of this manuscript.

Disclosure summary:

1. I, the designated corresponding author, on behalf of myself and my co-authors, hereby transfer and assign all right, title, and interest, including copyright and any moral rights, in and to the manuscript named in this submission (called the Work hereafter) to the Endocrine Society (ES). If ES ultimately declines to publish the Work in an ES journal, all rights in and to the Work will revert to the author(s).

2. I, and all co-authors, warrant that the Work intended for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration. We further warrant that the Work does not contain any material that is defamatory or the publication of which would violate any copyright or other personal, intellectual, property, contract, or proprietary right of any person or entity.

3. I warrant that each person listed as an author participated in the Work in a substantive way and is prepared to take public responsibility for it. All authors consent to the investigation of any improprieties that may be alleged regarding the Work. Each author further releases and holds harmless the Endocrine Society from any claim or liability that may arise therefrom.

4. I warrant that I am authorised to accept the terms of this agreement on behalf of myself and all co-authors.

I accept the terms of the agreement on behalf of myself and all co-authors.

The authors have nothing to disclose.

REFERENCES

1. Lee CD, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, Stanford FC, Kohl HW, Blair SN. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: The Aerobics Center Longitudinal Study. *Circulation.* 2011;**124**(23):2483-2490.
2. Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on all-cause mortality: A meta-analysis. *Prog in Cardiovasc Dis.* 2014;5**6**(4):382-390.
3. Blair SN, Kohl HW, Barlow CE, Gibbons LW. Physical fitness and all-cause mortality in hypertensive men. *Ann Med.* 1991;**23**(3):307-312.

4. Thompson DR, Obarzanek E, Franko DL, Barton BA, Morrison J, Biro FM, Daniels SR, Striegel-Moore RH. Childhood overweight and cardiovascular disease risk factors: The National Heart, Lung, and Blood Institute Growth and Health Study. *The J. Pediatr.* 2007;**150**(1):18-25.
5. Cruz ML, Shaibi GQ, Weigensberg MJ, Spruijt-Metz D, Ball GDC, Goran MI. Pediatric obesity and insulin resistance: Chronic disease risk and implications for treatment and prevention beyond body weight modification. *Ann. Rev. Nutr.* 2005;**25**(1):435-468.
6. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes.* 2007;**32**(1):1-11.
7. Eisenmann JC, Katzmarzyk PT, Perusse L, Tremblay A, Despres JP, Bouchard C. Aerobic fitness, body mass index, and CVD risk factors among adolescents: the Quebec family study. *Int J Obes Relat Metab Disord.* 2005;**29**(9):1077-1083.
8. Eisenmann JC, Wickel EE, Welk GJ, Blair SN. Relationship between adolescent fitness and fatness and cardiovascular disease risk factors in adulthood: the Aerobics Center Longitudinal Study (ACLS). *Am. Heart J.* 2005;**149**(1):46-53.
9. Eisenmann JC, Welk GJ, Ihmels M, Dollman J. Fatness, fitness, and cardiovascular disease risk factors in children and adolescents. *Med. Sci. Sports Exerc.* 2007;**39(**8):1251.
10. DuBose KD, Eisenmann JC, Donnelly JE. Aerobic fitness attenuates the metabolic syndrome score in normal-weight, at-risk-for-overweight, and overweight children. *Pediatrics.* 2007;**120(**5):e1262-e1268.
11. Burns R, Hannon JC, Brusseau TA, Shultz B, Eisenman P. Indices of abdominal adiposity and cardiorespiratory fitness test performance in middle-school students. *J Obes.* 2013;2013:912460.
12. Newnham J, Evans S, Michael C, Stanley F, Landau L. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet.* 1993;**342**(8876):887-891.
13. McDowell MA, Fryar CD, Hirsch R, Ogden CL. Anthropometric reference data for children and adults: US population, 1999–2002. *Adv Data.* 2005;**361**(361):1-5.
14. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11, Data from the national health survey.* 2002(246):1-190.
15. Campbell PT, Katzmarzyk PT, Malina RM, Rao D, Perusse L, Bouchard C. Prediction of physical activity and physical work capacity (PWC 150) in young adulthood from childhood and adolescence with consideration of parental measures. *AM J HUm Biol.* 2001;**13**(2):190-196.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. *Clin. Chem.* 1972; (6):499-502.
17. NCEP Expert Panel of Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics.* 1992;**89**:495-501.
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;**28**(7):412-419.
19. Ambrosini GL, Huang RC, Mori TA, Hands BP, O'Sullivan TA, de Klerk NH, Beilin LJ, Oddy WH. Dietary patterns and markers for the metabolic syndrome in Australian adolescents. *Nutr Metab Cardiovasc Dis..* 2010;**20**(4):274-283.
20. Ambrosini GL, De Klerk NH, O'Sullivan TA, Beilin LJ, Oddy WH. The reliability of a food frequency questionnaire for use among adolescents. *Eur J Clinl Nutr.* 2009;**63**(10):1251.

21. Tobin J. Estimation of Relationships for Limited Dependent Variables. *Econometrica.* 1958;**26**(1):24-36.
22. Sundström J, Neovius M, Tynelius P, Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. *BMJ.* 2011;342:d643.
23. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA.* 2004;**291**(17):2107-2113.
24. Brady TM, Fivush B, Flynn JT, Parekh R. Ability of blood pressure to predict left ventricular hypertrophy in children with primary hypertension. *J. Pediar.* 2008;**152**(1):73-78. e71.
25. Ayer J, Charakida M, Deanfield JE, Celermajer DS. Lifetime risk: childhood obesity and cardiovascular risk. *Eur. Heart J.* 2015;**36**(22):1371-1376.
26. Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R. European Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* 2012;**33**(13):1635-1701.
27. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs Jr DR, Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA.* 2003;**290**(23):3092-3100.
28. Jago R, Drews KL, McMurray RG, Thompspn D, Volpe SL, Moe EL, Jakicic JM, Pham TH, Bruecker S, Blackshear TB, Yin Z. Fatness, fitness, and cardiometabolic risk factors among sixth-grade youth. *Med. Sci. Sports Exerc.* 2010;**42**(8):1502-1510.
29. Ondrak KS, McMurray RG, Bangdiwala SI, Harrell JS. Influence of aerobic power and percent body fat on cardiovascular disease risk in youth. *J Adolesc Health.* 2007;**41**(2):146-152.
30. Nielsen GA, Andersen LBo. The association between high blood pressure, physical fitness, and body mass index in adolescents. *Prev. Med.* 2003;**36**(2):229-234.
31. Ruiz JR, Ortega FB, Loit HM, Veidebaum T, Sjöström M. Body fat is associated with blood pressure in school-aged girls with low cardiorespiratory fitness: the European Youth Heart Study. *J. Hypertens.* 2007;**25**(10):2027-2034.
32. Ruiz JR, Rizzo NS, Ortega FB, Loit HM, Veidebaum T, Sjöström M. Markers of insulin resistance are associated with fatness and fitness in school-aged children: the European Youth Heart Study. *Diabetologia.* 2007;**50**(7):1401-1408.
33. Sun SS, Liang R, Huang TTK, Daniels SR, Arslanian S, Liu K, Grave GD, Siervogel RM. Childhood obesity predicts adult metabolic syndrome: the Fels Longitudinal Study. *J. Pediatr.* 2008;**152**(2):191-200. e191.
34. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. *Pediatrics.* 2008;**122**(1):198-208.
35. Heyman E, Briard D, Dekerdanet M, Gratas-Delamarche A, Delamarche P. Accuracy of physical working capacity 170 to estimate aerobic fitness in prepubertal diabetic boys and in 2 insulin dose conditions. *J Sports Med Phys Fitness*. 2006;**46**(2):315.
36. Ventura AK, Loken E, Mitchell DC, Smiciklas-Wright H, Birch LL. Understanding Reporting Bias in the Dietary Recall Data of 11-Year-Old Girls. *Obesity.* 2006;**14**(6):1073-1084.
37. Redwine KM, Acosta AA, Poffenbarger T, Portman RJ, Samuels J. Development of hypertension in adolescents with pre-hypertension. *J. Pediatr.* 2012;**160**(1):98-103.
38. Knapen J, Vancampfort D, Moriën Y, Marchal Y. Exercise therapy improves both mental and physical health in patients with major depression. *Disabil Rehabil.* 2015;**37**(16):1490-1495.

39. Berchicci M, Pontifex MB, Drollette ES, Pesce C, Hillman CH, Di Russo F. From cognitive motor preparation to visual processing: The benefits of childhood fitness to brain health. *Neuroscience.* 2015;**298**:211-219.
40. Robsahm TE, Falk RS, Heir T, Sandvik L, Vos L, Erikssen JE, Tretli S. Measured cardiorespiratory fitness and self-reported physical activity: associations with cancer risk and death in a long-term prospective cohort study. *Cancer Med.* 2016;**5**(8):2136-2144.

Fatness was positively associated with systolic BP (coefficient=0.19; p<0.001), whereas no associations between fitness and systolic BP were observed. These effects did not vary by sex (Figure 1a). Fatness was inversely associated with HDL-C in both males and females (coefficient= -0.006; p<0.001), whereas, fitness was positively associated with HDL-C in females only (coefficient=0.08; p=0.03) (Figure 1b). Fatness was positively associated with HOMA-IR to a greater magnitude (log coefficient=-0.2; p<0.001) compared to the inverse association of fitness with HOMA-IR (log coefficient=-0.18; p<0.001). These effects did not vary by sex (Figure 1c). Figure 1a-1c were generated from unadjusted models. Abbreviations: BP: blood pressure; HDL-C: High density lipoprotein-cholesterol HOMA-IR: Homeostatic model of insulin resistance; OC: oral contraceptives.

Table 1. Characteristics of participants at 17 years

Measure	Females N=544	Males n= 587	P value
Anthropometry			
Waist circumference (cm)	77.7 (76.8, 78.7)	80.5 (79.6, 81.4)	<0.001
Waist circumference (≥90th percentile) (%)	9.6 (7.3, 12.4)	10.7 (8.5, 13.5)	0.38
Weight (kg)	63.4 (62.3, 64.5)	72.0 (70.9, 73.2)	<0.001
Height (m)	1.7 (1.6, 1.7)	1.9 (1.8, 1.8)	<0.001
BMI (kg/m^2)	22.9 (22.6, 23.4)	22.6 (22.3, 22.9)	0.12
BMI (≥90th percentile) (%)	9.2 (6.9, 11.9)	8.4 (6.4, 10.9)	0.44
Fitness (PWC_{170}) (W)	100.1 (98.1, 102.2)	155.1 (151.6, 158.6)	<0.001
Fitness/body weight (W/kg)	1.6 (1.5, 1.7)	2.2 (2.1, 2.2)	<0.001
Fitness/body weight (lowest tertile)	0.8 (0.6, 0.9)	1.3 (1.1, 1.4)	<0.001
Biochemistry			
Cholesterol (mmol/L)	4.3 (4.2, 4.4)	3.9 (3.8, 4.0)	<0.001
Triglycerides (mmol/L)	1.0 (0.9, 1.1)	1.1 (1.0,1.1)	0.23
Triglycerides (≥ 1.47 mmol) (%)	12.5 (9.7, 15.9)	18.3 (15.2, 21.9)	0.02
HDL-C (mmol/L)	1.4 (1.3, 1.5)	1.2 (1.1, 1.3)	<0.001
HDL-C (≤1.04 mmol/L (%)	9.7 (7.5, 12.6)	22.8 (19.6, 26.4)	<0.001
LDL-C (mmol/L)	2.4 (2.4, 2.5)	2.2 (2.2, 2.3)	<0.001
LDL-C (≥ 3.36 mmol/L) (%)	8.5 (6.2, 11.4)	5.1 (3.5, 7.3)	0.05
Glucose (mmol/L)	4.6 (4.6, 4.7)	4.8 (4.8, 4.9)	<0.001
Insulin (mU/L)	9.5 (8.8, 10.2)	8.5 (8.0, 9.1)	0.03
HOMA-IR	2.1 (1.9, 2.2)	1.9 (1.7, 2.0)	0.12
hs C-reactive protein (mg/L)	2.3 (1.7, 2.9)	1.4 (1.0, 1.7)	0.009
Blood Pressure			
Systolic BP (mmHg)	108.4 (107.6, 109.1)	117.8 (117.0, 118.5)	<0.001
Diastolic BP (mmHg)	59.3 (58.8, 59.9)	58.1 (57.6, 58.7)	0.002
Pre-hypertension/hypertension status (%)	15.2%	16.7%	0.63
Lifestyle factors (%)			
Alcohol drinker[&]	49 (46, 54)	51 (47.1, 55)	0.71
Oral contraceptive use	13.9 (12.1, 16)		
Smoker[^]	15.3 (12.5, 18.6)	15.4 (12.6, 18.6)	0.96
Healthy dietary pattern	0.1 (0.03, 0.2)	-0.1 (-0.2, -0.02)	<0.001
Western dietary pattern	-0.5 (-0.6, -0.4)	0.09 (-0.01, 0.2)	<0.001
Annual family income			
≤ A$ 35,000	13.1 (10.3, 16.4)	12.2 (9.6, 15.3)	
A$ 35,001 – ≤78,000	33.3 (29.1, 37.7)	33.6 (29.6, 27.9)	
> A$ 78,000	53.6 (49.0, 58.2)	54.2 (49.8, 58.5)	

Data are based on participants present in either set of analyses and presented as mean or for categorical variables as a percentage (95% CI). Abbreviations: BMI: Body Mass Index; BP: blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein ch0.olesterol; HOMA-IR: Homeostatic model of assessment of insulin resistance; W: watts; *Non-sex specific systolic BP ≥90th percentile; [&]Consumer of alcohol at any level over the last 7 days; ^ Smoking ≥1 cigarettes in a week

Table 2. Linear regression analyses examining the influence of fatness and fitness on BP at 17 years

	Systolic blood pressure n=1128				Diastolic blood pressure n=1128			
Model 1	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**
OC using females	3.56	1.93, 5.18	<0.001		1.65	0.50, 2.79	0.005	
Males	10.28	8.94, 11.62	<0.001		0.35	-0.58, 1.29	0.46	
Fatness	**0.19**	**0.14, 0.24**	**<0.001**	**0.20**	**-0.03**	**-0.07, 0.003**	**0.07**	**N/A**
Fitness	**-0.57**	**-1.78, 0.63**	**0.35**	**N/A**	**-1.57**	**-2.35, 0.79**	**<0.001**	**-0.16**
Constant	93.62	88.60, 98.64	<0.001		63.92	60.37, 67.46	<0.001	
Model 2								
OC using females	3.55	1.88, 5.21	<0.001		1.55	0.39, 2.70	0.009	
Males	10.22	8.76, 11.67	<0.001		0.17	-0.86, 1.20	0.75	
Fatness	**0.18**	**0.14, 0.24**	**<0.001**	**0.20**	**-0.03**	**-0.07, 0.002**	**0.06**	**N/A**
Fitness	**-0.76**	**-2.00, 0.48**	**0.23**	**N/A**	**-1.59**	**-2.39, 0.80**	**<0.001**	**-0.16**
Alcohol	1.40	0.32, 2.48	0.01		0.73	-0.03, 1.49	0.05	
Smoking	-1.16	-2.67, 0.35	0.13		-0.93	-2.08, 0.22	0.11	
Diet- Healthy	-0.12	-0.84, 0.60	0.75		-0.14	-0.62, 0.33	0.55	
Diet- Western	0.23	-0.55, 1.01	0.57		0.24	-0.33, 0.80	0.41	
Middle family income	-0.31	-2.14, 1.51	0.74		0.08	-1.28, 1.43	0.97	
High family income	0.33	-1.42, 2.08	0.71		-0.20	-1.51, 1.11	0.77	
Constant	93.61	88.35, 98.87	<0.001		64.08	60.39, 67.78	<0.001	

Model 1: Base model adjusting for 3 level sex variable only
Model 2: Model 1 with further adjustment for potential lifestyle confounders of alcohol use, smoking, dietary pattern and family income
Abbreviations: CI: confidence interval; OC: oral contraceptives.
In model 1 adjusting for sex and OC use, fatness was positively associated with systolic BP (coefficient: 0.19; p<0.001). After adjusting for additional potential confounders, systolic BP remained positively associated with fatness (coefficient: 0.18; p<0.001). Fitness was not associated with systolic BP in the unadjusted or confounder adjusted model. Fatness was not significantly associated with diastolic BP whereas fitness was inversely associated with diastolic BP (coefficient= -1.57; p<0.001). Further adjustment for lifestyle factors did not substantially change the coefficients.

Table 3. Linear regression analyses examining the influence of fatness and fitness with HDL-C or triglycerides at 17 years

		HDL-C n=963			Log triglycerides n=936*			
Model 1	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**

Males	-0.04	-0.18, 0.09	0.52		0.007	-0.05, 0.07	0.83	
Fatness	**-0.006**	**-0.008, -0.004**	**<0.001**	**-0.23**	**0.009**	**0.007, 0.01**	**<0.001**	**0.24**
Fitness	**0.08**	**0.007, 0.15**	**0.03**	**0.15**	**-0.02**	**-0.07, 0.04**	**0.49**	**N/A**
Fitness*sex	**-0.08**	**-0.16, -0.005**	**0.04**		N/A	N/A	N/A	
Constant	1.75	1.58, 1.93	<0.001		-0.75	-0.99, -0.50	<0.001	
Model 2								
Males	-0.04	-0.18, 0.09	0.55		0.007	-0.06, 0.07	0.84	
Fatness	**-0.006**	**-0.008, -0.005**	**<0.001**	**-0.24**	**0.009**	**0.006, 0.01**	**<0.001**	**0.24**
Fitness	**0.08**	**0.005, 0.15**	**0.03**	**0.17**	**-0.02**	**-0.07, 0.04**	**0.59**	**N/A**
Fitness*sex	**-0.08**	**-0.16, -0.008**	**0.03**	**N/A**	N/A	N/A	N/A	
Alcohol	0.02	-0.01, 0.06	0.24		0.02	-0.03, 0.08	0.44	
Smoking	-0.02	-0.08, 0.03	0.39		0.11	0.02, 0.19	0.01	
Diet-Healthy	-0.002	-0.02, 0.02	0.83		-0.02	-0.05, 0.02	0.37	
Diet-Western	0.002	-0.02, 0.03	0.88		-0.008	-0.05, 0.03	0.69	
Middle family income	0.02	-0.04, 0.08	0.52		0.002	-0.10, 0.11	0.97	
High family income	0.01	-0.05, 0.07	0.74		-0.01	-0.11, 0.09	0.82	
Constant	1.74	1.56, 1.93	<0.001		-0.75	-1.00, -0.50	<0.001	

Model 1: Base model adjusting for sex only
Model 2: Model 1 with further adjustment for potential lifestyle confounders of alcohol use, smoking, dietary pattern and family income
*Non-fasting individuals removed
Abbreviations: CI: confidence interval; HDL-C: high density lipoprotein-cholesterol.

Fatness was inversely associated with HDL-C in both males and females (coefficient= -0.006 p<0.001). Fitness was positively associated with HDL-C in females only (coefficient: 0.08; p=0.03). The standardised beta coefficients showed that in females, fatness had a greater effect on HDL-C (beta coefficient: -0.23) compared with fitness (beta coefficient: 0.15). These findings did not change after the inclusion of potential confounders (Table 3, Model 2). Fatness was positively associated with triglycerides in both sexes (log coefficient: 0.009, p<0.001) (Table 3, Model 1). This association was not altered after the inclusion of potential confounders.

Table 4. Linear regression analyses examining the influence of fatness and fitness with cholesterol or LDL-C at 17 years

		Cholesterol n=963			LDL-C n=963			
Model 1	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**
Males	-0.35	-0.46, -0.23	<0.001		-0.18	-0.28, -0.07	0.001	
Fatness	**0.004**	**-0.00002, 0.009**	**0.05**	**N/A**	**0.005**	**0.002, 0.009**	**0.007**	**0.10**
Fitness	**-0.04**	**-0.15, 0.06**	**0.43**	**N/A**	**-0.04**	**-0.14, 0.05**	**0.35**	**N/A**
Constant	4.02	3.60, 4.45	<0.001		2.06	1.68, 2.45	<0.001	
Model 2								
Males	-0.34	-0.47, -0.21	<0.001		-0.16	-0.28, -0.05	0.004	
Fatness	**0.004**	**-0.0002, 0.009**	**0.06**	**N/A**	**0.006**	**0.002, 0.01**	**0.007**	**0.10**
Fitness	**-0.04**	**-0.15, 0.07**	**0.46**	**N/A**	**-0.04**	**-0.14, 0.05**	**0.38**	**N/A**
Alcohol	0.008	-0.09, 0.10	0.87		-0.01	-0.10, 0.08	0.82	
Smoking	0.01	-0.13, 0.16	0.86		-0.04	-0.18, 0.10	0.57	
Diet- Healthy	0.004	-0.05, 0.06	0.88		0.01	-0.04, 0.06	0.64	
Diet-Western	-0.01	-0.08, 0.06	0.72		-0.02	-0.08, 0.04	0.61	
Middle family income	-0.04	-0.22, 0.14	0.62		-0.04	-0.21, 0.13	0.64	
High family income	-0.06	-0.24, 0.11	0.47		-0.05	-0.21, 0.12	0.56	
Constant	4.06	3.61, 4.51	<0.001		2.09	1.69, 2.51	<0.001	

Model 1: Base model adjusting for sex only

Model 2: Model 1 with further adjustment for potential lifestyle confounders of alcohol use, smoking, dietary pattern and family income
Abbreviations: CI: confidence interval; LDL-C: low density lipoprotein-cholesterol.
Neither fatness nor fitness was significantly associated with cholesterol in both unadjusted and adjusted models. Fatness was positively associated with LDL-C in both sexes (coefficient: 0.005, p=0.007). This association was not altered after the inclusion of potential confounders. Fitness was not associated with LDL-C in unadjusted or adjusted analyses.

Table 5. Linear regression analyses examining the influence of fatness and fitness with HOMA-IR or hs-CRP at 17 years

	Log HOMA-IR n=936*				Log hs-CRP n=950[&]			
Model 1	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**	**Regression Coefficient**	**95% CI**	**P value**	**Beta Coefficient**
Males	-0.03	-0.12, 0.07	0.59		-0.70	-0.93, -0.49	<0.001	
Fatness	**0.02**	**0.01, 0.02**	**<0.001**	**0.33**	**0.05**	**0.04, 0.06**	**<0.001**	**0.35**
Fitness	**-0.18**	**-0.27, -0.09**	**<0.001**	**-0.18**	**-0.06**	**-0.26, 0.13**	**0.52**	**N/A**
Constant	-0.80	-1.18, -0.43	<0.001		-3.79	-4.66, -2.92	<0.001	
Model 2								
Males	-0.06	-0.6, 0.05	0.28		-0.70	-0.92, -0.48	<0.001	
Fatness	**0.02**	**0.01, 0.02**	**<0.001**	**0.36**	**0.04**	**0.03, 0.05**	**<0.001**	**0.34**
Fitness	**-0.15**	**-0.24, -0.06**	**0.001**	**-0.13**	**-0.07**	**-0.26, 0.13**	**0.50**	**N/A**
Alcohol	-0.13	-0.21, -0.04	0.002		N/A	N/A	N/A	
Smoking	0.07	-0.06, 0.19	0.30		0.36	0.11, 0.60	0.004	
Diet- Healthy	-0.02	-0.08, 0.03	0.43		N/A	N/A	N/A	
Diet-Western	0.02	-0.05, 0.10	0.50		N/A	N/A	N/A	
Middle family income	0.04	-0.10, 0.17	0.61		N/A	N/A	N/A	
High family income	-0.02	-0.16, 0.11	0.74		N/A	N/A	N/A	
Constant	-0.81	-1.20, -0.42	<0.001		-3.78	-4.64, -2.92	<0.001	

Model 1: Base model adjusting for sex only
Model 2: Model 1 with further adjustment for potential lifestyle confounders of alcohol use, smoking, dietary pattern and family income
*Non-fasting individuals removed
[&]Tobit regression
Abbreviations: CI: confidence interval; HOMA-IR: homeostatic model of insulin resistance; hs-CRP: high sensitivity C-reactive protein.
Fatness was positively associated with HOMA-IR (log coefficient: 0.02; p<0.001) after adjusting for sex, whereas fitness was inversely associated with HOMA-IR (log coefficient: -0.18; p<0.001). The standardised beta coefficients showed that fatness had a greater effect on HOMA-IR (beta coefficient: 0.33) compared with fitness (beta coefficient: -0.16). These effects did not vary by sex. After further adjustment for lifestyle factors, these effects were unchanged. Fatness was positively associated with hs-CRP in both sexes (log coefficient: 0.05, p<0.001) and this association was not altered after the inclusion of confounders. Fitness was not associated with hs-CRP in either model.

Figure 1a. Fatness vs fitness with systolic BP for males, OC using females and non-OC using females

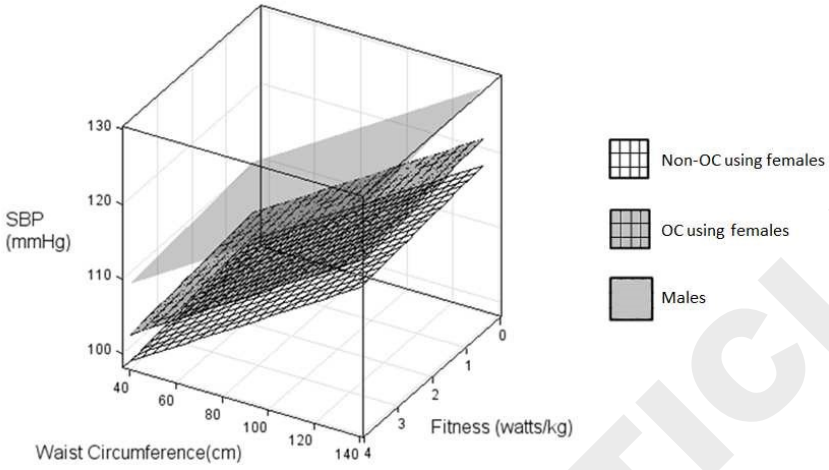

Figure 1b. Fatness vs fitness with HDL-C for males and females

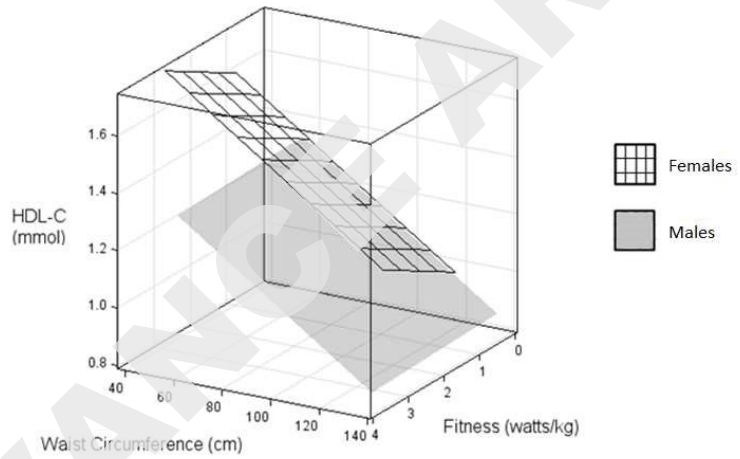

Figure 1c. Fatness vs fitness with HOMA-IR for males and females